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Date: December 10, 2008 Rebecca A. Bellas

Rebecca A. Bellas

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:			
Applicant:	Hedding-Eckerich, et al.	Examiner:	Patrick Lewis
Serial No:	10/511,026	Art Unit:	1623
Filing Date:	May 31, 2005		

Title: USE OF PYRIMIDINE NUCLEOTIDES FOR THE TREATMENT OF AFFECTIONS OF THE PERIPERAL NERVOUS SYSTEM

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Dear Sir:

Appellants' representative submits this brief in connection with an appeal of the above-identified patent application and in response to the Advisory Action dated August 26th, 2008 and Notification dated November 17th, 2008.

I. Table of Contents

II. Real Party in Interest (37 C.F.R. § 41.37(c)(1)(i))

The real party in interest in the present appeal is Trommsdorff, GmbH, & Co. KG Arzneimittel; the assignees of the present application.

II. Related Appeals and Interferences (37 C.F.R. § 41.37(c)(1)(ii))

Appellants, appellants' legal representative, and/or the assignee of the present application are not aware of any appeals or interferences which may be related to, will directly affect, or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. Status of Claims (37 C.F.R. § 41.37(c)(1)(iii))

Claims 1-17 stand rejected by the Examiner. The rejection of claims 1-17 is being appealed.

IV. Status of Amendments (37 C.F.R. § 41.37(c)(1)(iv))

An amendment to dependant claim 2 was proposed subsequent to the Final Office Action (dated February 25th, 2008); to rectify the patentable subject matter requirement and indefiniteness under 35 USC §101 and §112, second paragraph. This subsequent amendment was not entered for the purposes of appeal (Advisory Action dated August 26th, 2008).

V. Summary of Claimed Subject Matter (37 C.F.R. § 41.37(c)(1)(v))

Independent Claim 1

Independent claim 1 relates to a method of using uridine-5'-monophosphate or cytidine-5'-monophosphate for the treatment of affections of the peripheral nervous system and/or for the stimulation of the regeneration of nerves. The aforementioned nucleotides herein referred to as UMP and CMP respectively, are known to contribute to the regeneration of damaged nerves (pg. 2, lines 10-15). The external application of

UMP or CMP on patients with polyneuropathies led to amelioration of typical symptoms (pg. 2, lines 16-17; Results, Tables 1 and 2).

Dependent Claim 2

Dependent Claim 2 recites the method of claim 1, wherein uridine-5'-monophosphate is administered to a patient in need thereof. Claim 2 defines the method of claim1 with respect to the administration of UMP. The method requires the use of a single nucleotide for the treatment of affections of the peripheral nervous system and/or the stimulation of nerve regeneration (pg. 3, lines 24-27) contrary to previous methods that require combination therapies (pg. 3, lines 14-17). Therefore, claim 2 incorporates all the features of independent claim 1.

Independent Claim 6

Independent claim 6 relates to a method of using UMP or CMP to make a pharmaceutical composition for the treatment of affections of the peripheral nervous system and/or for the stimulation of the regeneration of nerves (pg. 4, lines 14-24).

Independent Claim 7

Independent claim 7 relates to a pharmaceutical composition of either UMP or CMP. Either nucleotide can comprise a pharmaceutically active ingredient that can be composed with physiologically acceptable carriers, adjuvants and/or diluents. Compositions can be tablets, film tablets, coated tablets, capsules, pills, powders, solutions, dispersions, suspensions, deposits or inhalation solutions; and comprised of known adjuvants such as:

inert dilutors like dextrose, sugar, sorbitol, mannite, polyvinylpyrrolidone, disintegrating agents like corn starch or alginic acid, binders like starch or gelatin, lubricants like magnesium stearate or talc and/or agents for achieving a deposit effect like carboxypolymethylene,

carboxymethylcellulose, cellulose acetate phthalate or polyvinyl acetate.

The tablets can also consist of several layers (pg 5, lines 1-11).

VI. Grounds of Rejection to be Reviewed (37 C.F.R. § 41.37(c)(1)(vi))

A. Whether claims 2, 10-12, and 15-16 are patentable under 35 U.S.C. § 112, second paragraph, in the description of the claimed subject matter.

B. Whether claims 1-17 are patentable under 35 U.S.C. § 103(a) over Connolly et al literature review (TiPS, 1999, Vol. 20, pgs. 218-225).

VII. Argument (37 C.F.R. §41.37(c)(1)(vii))

A. Rejection of Claims 2, 10-12, and 15-16 under 35 U.S.C. § 112

Claims 2, 10-12, and 15-16 stand rejected for indefiniteness. The Examiner contends that the phrase in dependant claim 2 "characterized in that uridin-5'-monophosphate is concerned" renders the claim indefinite and unclear. However, the Description clearly states that the invention relates to the use of a pyrimidine nucleotide for the treatment of affections of the peripheral nervous system as well as the stimulation of the regeneration of nerves (pg 1, lines 6-8). Since "uridin-5'-monophosphate" is a pyrimidine nucleotide and the disclosed treatments are features of claim 1, it is respectfully requested that the rejection of claims 2, 10-12, and 15-16 be reversed. Applicant's also note "uridin-5'-monophosphate" as read in claim 2 should read "uridine-5'-monophosphate".

B. Rejection of Claims 1-17 Under 35 U.S.C. § 103(a)

Claims 1-17 stand rejected under 35 U.S.C. § 103(a) over Connolly et al literature review (TiPS, 1999, Vol. 20, pgs. 218-225). Connolly et al is cited for alleged teachings concerning the roles for the pyrimidine nucleoside uridine and its nucleotide derivatives in the regulation of some biological systems. Moreover, Connolly asserts overly ambitious and broadly speculative suggestions regarding the possibility of

therapeutic targets such as respiratory, circulatory, reproductive, and nervous systems, as well as the treatments of cancer and HIV infection.

Obviousness determinations under § 103 are weighed after several factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed the claimed subject matter and the prior art, (3) the level of skill in the art, and (4) secondary considerations. *Graham v. John Deere Co.* of *Kansas City,* 383 U.S. 1, 17-18 (1966).

a. Overview of the Invention

The subject claims relate to a method of using pyrimidine nucleotides, uridine-5'-monophosphate or cytidine-5'-monophosphate for the treatment of affections of the peripheral nervous system and/or for the stimulation of the regeneration of nerves, comprising administration to a patient. Nucleic acids represent the basis of nerve regeneration. Nucleosides are incorporated by the nerve cells and converted into nucleotides. Nucleotides get into the axons, which decisively participate in the regeneration process. Cytidine and uridine thereby effect the new synthesis of structural components of the nerve cell (pg. 2, lines 10-15)(*citing* J. Cervos-Navarro, Ärzte Zeitung, 1992, No. 131, pg. 2). The claims are directed at uridine-5'-monophosphate or cytidine-5'-monophosphate, and a pharmaceutical composition consisting of uridine-5'-monophosphate or cytidine-5'-monophosphate for affections of the peripheral nervous system concern polyneuropathies, neuritides and/or myopathies.

b. The cited art does not teach or suggest each and every claim feature.

Claim 1 recites a method of using uridine-5'-monophosphate or cytidine-5'-monophosphate for the treatment of affections of the peripheral nervous system and/or for the stimulation of the regeneration of nerves, comprising administering uridine-5'-monophosphate or cytidine-5'-monophosphate to a patient in need thereof.

While Connolly does only discuss relatively few molecules, the studies cited in Connolly (specifically those relating in some way to the peripheral nervous system) at most implicate a role for nucleotides as neurotransmitters, ***but do NOT suggest a particular mechanism of action or implicate a role of claimed molecules in***

neuroregeneration. Connolly, at most, merely postulates a role for uridine (and NOT cytidine) as an inhibitory neuromodulator (pg. 221, col. 1, para. 3).

Among the electrophysiological studies cited by Connolly, it was found that nucleotides (including CMP and UMP) altered the polarity in amphibian sympathetic ganglia and in rat superior cervical ganglia. These observations suggest that nucleotides may have roles as neurotransmitters, ***but did NOT implicate CMP or UMP involvement in nerve or muscle regeneration***. Conversely the Example of the application demonstrates (see page 7 of the present application), for the first time, the clinical usefulness in humans of short term treatment with a single pyrimidine and that the mechanism of action of the treatment with a single pyrimidine according to present invention is nerve regeneration. The mechanism of stimulating regeneration, as claimed in independent claim 1, occurs via synthesis of membrane phospholipids, such as sphingolipids and phosphatidylcholine. Connolly fails to teach or suggest stimulating regeneration by synthesis of membrane phospholipids. Hence, because Connolly only suggests roles as neurotransmitters, it would not have formed the basis for obviousness among individuals skilled in the art to use cytidine or uridine in a method and composition as claimed in independent claims 1 and 7 respectively.

Connolly asserts, in light of Gallai et al, that uridine dramatically promoted the recovery from the neural regeneration produced by diabetic neuropathy. This was an electrophysiological study that alleged improvement of motor and sensory responses in a small sample size (n=20) receiving treatment after 60, 120, and 180 day intervals. The study based its conclusions upon measurements in the small 120 day experimental group compared only to the 90 day control group (also n=20). Although the amplitudes of motor and sensory responses appeared improved in individuals that received UMP, ***this study also did not identify a mechanism for improvement, it did not measure nerve growth, nor did it implicate UMP or CMP as being involved in regeneration*** (CMP was not used in the study). Moreover, such assertions are suspect at best over shoddy experimental design, mainly small sample sizes.

The Examiner concedes (Office Action, February 25, 2008) that while Connolly et al may teach or suggest some therapeutic benefits of uridine and its nucleotides, it does so broadly. As suggested by the Examiner, the cited document only provides general

information regarding possible effects of uridine on the nervous system. The studies cited in Connolly implicate a role for nucleotides as neurotransmitters, but do not suggest a particular mechanism of action. Moreover, Connolly et al fails to suggest any elements set forth in the claims. Connolly draws a general and speculative conclusion that UMP may prove therapeutic utility in treating neurodegenerative disorders, but does not teach or suggest how. The studies cited in Connolly only show electrophysiological changes in some nerve cells and at best suggest possible roles for nucleotides only as neurotransmitters. ***Nucleotides were not implicated in tissue regeneration***, nor was CMP tested in the diabetic neuropathy study. Therefore it would NOT have been obvious to an individual skilled in the art to use UMP or CMP to treat polyneuropathies, neuritides and/or myopathies as claimed.

Further, independent claim 7 recites a pharmaceutical composition consisting of uridine-5'-monophosphate or cytidine-5'-monophosphate as pharmaceutically active ingredient optionally together with physiologically acceptable carriers, adjuvants and/or diluents. Connolly neither teaches nor suggests any compositions for administration of CMP or UMP. Since the documents cited in the Connolly literature review do NOT teach or suggest a method or use of a composition of UMP or CMP to treat polyneuropathies, neuritides and/or myopathies, or method thereof, a skilled artisan would NOT have been motivated by alleged features of the Examiner's cited document. Therefore, it is respectfully requested that the obviousness rejection be withdrawn.

c. <u>The methodology employed in the cited art teaches away from using the single compound UMP or the single compound CMP for the regeneration of nerves</u>

Concerning independent claim 1, a method of using uridine-5'-monophosphate or cytidine-5'-monophosphate for the treatment of affections of the peripheral nervous system and/or for stimulating the regeneration of nerves, comprising administering uridine-5'-monophosphate or cytidine-5'-monophosphate to a patient in need thereof. The International Search Report contains three closely related documents from the same university research group (Wattig).

In D1 it is clearly mentioned that only the combination of UMP and CMP is

effective in the regeneration of nerves; and that the single compound UMP or the single compound CMP do not show any effect on the regeneration of nerves (Z. Klin. Med. 1991, 46(19), 1371-1373). Consequently, there is a clear state of the art that describes that the single compound UMP or the single compound CMP as having no effect on regeneration of nerves. A person having ordinary skill in the art would certainly act on the assumption that both compounds UMP and CMP together produce a combined or synergistic effect. Since the cited art teaches away from using the single compound UMP or the single compound CMP for the regeneration of nerves, a person having ordinary skill in the art would not have deemed the subject invention obvious. Hence, it is respectfully requested that the rejection of claims 1-17 be reversed.

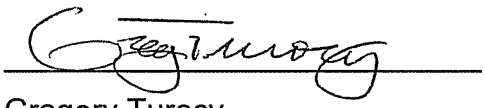
C. Conclusion.

For at least the above reasons, the claims currently under consideration are believed to be patentable over the cited references. Accordingly, it is respectfully requested that the rejections of claims 1-17 be reversed.

If any additional fees are due in connection with this document, the Commissioner is authorized to charge those fees to Deposit Account No. 50-1063.

Respectfully submitted,

AMIN, TUROCY & CALVIN, LLP



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VIII. Claims Appendix (37 C.F.R. §41.37(c)(1)(viii))

What is claimed is:

1. (rejected) A method of using uridine-5'-monophosphate or cytidine-5'-monophosphate for the treatment of affections of the peripheral nervous system and/or for the stimulation of the regeneration of nerves, comprising administering uridine-5'-monophosphate or cytidine-5'-monophosphate to a patient in need thereof.

2. (rejected) The method according to claim 1, characterized in that uridin-5'-monophosphate is concerned.

3. (rejected) The method according to claim 1, wherein the affections of the peripheral nervous system concern polyneuropathies, neuritides and/or myopathies.

4. (rejected) The method according to claim 3, wherein the polyneuropathies, neuritides and myopathies concern degenerative diseases of the spinal column, diabetic polyneuropathies, polyneuropathies after alcohol abusus, other toxic polyneuropathies, facial nerve paresis, face neuralgias, multiple sclerosis, root neuritides, cervical syndrome, shoulder-arm syndrome, ischialgia, lumbago, intercostals neuralgia, trigeminus neuralgia and/or herpes zoster.

5. (rejected) The method according to claim 1, wherein uridine-5'-monophosphate or cytidine-5'-monophosphate is administered in a daily dose rate of 1 100 mg.

6. (rejected) A method of using uridine-5'-monophosphate or cytidine-5'-monophosphate for the manufacture of a pharmaceutical composition for the treatment of affections of the peripheral nervous system and/or for the stimulation of the regeneration of nerves, comprising adding uridine-5'-monophosphate or cytidine-5'-monophosphate to a pharmaceutical composition.

7. (rejected) Pharmaceutical composition consisting of uridine-5'-monophosphate or cytidine-5'-monophosphate as pharmaceutically active ingredient optionally together with physiologically acceptable carriers, adjuvants and/or diluents.

8. (rejected) Pharmaceutical composition according to claim 7, wherein the single pharmaceutical composition contains uridine-5'-monophosphate or cytidine-5'-monophosphate in a concentration of 1 - 100 mg.

9. (rejected) Pharmaceutical composition according to claim 7, wherein the pharmaceutical composition is suitable for oral application or injection.

10. (rejected) The method according to claim 2, wherein the affections of the peripheral nervous system concern polyneuropathies, neuritides and/or myopathies.

11. (rejected) The method according to claim 10, wherein the polyneuropathies, neuritides and myopathies concern degenerative diseases of the spinal column, diabetic polyneuropathies, polyneuropathies after alcohol abusus, other toxic polyneuropathies, facial nerve paresis, face neuralgias, multiple sclerosis, root neuritides, cervical syndrome, shoulder-arm syndrome, ischialgia, lumbago, intercostals neuralgia, trigeminus neuralgia and/or herpes zoster.

12. (rejected) The method according to claim 2, wherein uridine-5'-monophosphate or cytidine-5'-monophosphate is administered in a daily dose rate of 1 - 100 mg.

13. (rejected) The method according to claim 3, wherein uridine-5'-monophosphate or cytidine-5'-monophosphate is administered in a daily dose rate of 1 - 100 mg.

14. (rejected) The method according to claim 4, wherein uridine-5'-monophosphate or cytidine-5'-monophosphate is administered in a daily dose rate of

1 - 100 mg.

15. (rejected) The method according to claim 10, wherein uridine-5'-monophosphate or cytidine-5'-monophosphate is administered in a daily dose rate of 1 - 100 mg.

16. (rejected) The method according to claim 11, wherein uridine-5'-monophosphate or cytidine-5'-monophosphate is administered in a daily dose rate of 1 - 100 mg.

17. (rejected) Pharmaceutical composition according to claim 8, wherein the pharmaceutical composition is suitable for oral application or injection.

IX. Evidence Appendix (37 C.F.R. §41.37(c)(1)(ix))

None

X. Related Proceedings Appendix (37 C.F.R. §41.37(c)(1)(x)

None.